REMARKS

Following entry of this amendment, claims 1-3, 5-7, 11, 25, and 26 will be pending in this application. Claims 4, 10, and 21-24 are canceled without prejudice, and claims 1, 11, and 25 are currently amended. Support for the amendments can be found throughout the specification and claims as originally filed, e.g., at Fig. 1 and paragraphs [0011] ("tumor progression (recurrence)") and [0025] ("glioma"). No new matter has been added.

The amendment to the specification corrects an obvious error in the original. See the Declaration of Dr. John S. Yu Under 37 CFR § 1.132, submitted herewith. The Declaration demonstrates that one skilled in the art would recognize the error and its correction. Therefore, no new matter has been added by the amendment to the specification.

Examiner Interview

Applicants thank Examiner Goddard for holding an interview with Mr. J. Peter Fasse and the undersigned on September 15, 2009. During the interview, the current rejections for alleged obviousness were discussed.

35 USC § 103

Claims 1-3, 5, 10, 11, 25, and 26 were rejected as allegedly being unpatentable over U.S. Patent Application Publication 2002/0119121 ("Vitiello"), in view of Knutson, 2002, Curr. Opin. Mol. Ther., 4:403-407 ("Knutson") and Friedman et al., 2000, Clin. Cancer Res., 6:2585-97 ("Friedman"). Applicants respectfully traverse.

For at least the reasons of record, applicants do not concede that the Office has established a *prima facie* case of obviousness of the presently pending claims, that *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) is relevant to the currently pending claims, or that there was not a long-felt but unsolved need for effective central nervous system therapies. Even if the Office were to have established a *prima facie* case of obviousness, applicants have provided unexpected results that would rebut such a case.

Applicants' experimental results described in the specification are truly unexpected, as appears to be acknowledged by the Office action at pages 15-16: "the instant application demonstrates significant increases in time to progression for patients who received DC vaccine followed by chemotherapy administered at the time of recurrence." As described in Examples 1 and 2 of the present application, newly diagnosed glioblastoma multiforme (GBM) patients were administered surgical resection and standard radiation therapy, followed by either administration of chemotherapy or vaccination with DCs ([0044][1], Fig. 1A). Both the vaccine and chemotherapy groups had similar times of progression to an initial disease recurrence ([0046], Fig. 1B). Following an initial recurrence, patients in the vaccine+chemotherapy group were then administered a course of chemotherapy (see Fig. 1A). Strikingly, the average time to subsequent recurrence in patients administered chemotherapy following vaccination (about 13 months) was significantly increased compared to both initial recurrence in all groups (about 7-8 months) and the subsequent recurrences in the vaccine alone (about 6 months) and chemotherapy alone (about 3 months) groups (see Fig. 1B). Therefore, administration of chemotherapy following vaccination and subsequent tumor recurrence provided a significant delay in progression of the disease as compared to chemotherapy or vaccination alone. This result is unexpected even in view of the combined disclosures of Vitiello, Knutson, and Friedman.

Additionally, GBM patients receiving chemotherapy after vaccination and subsequent tumor recurrence enjoyed significantly prolonged survival relative to patients receiving either treatment individually ([0045], Figs. 2 and 5). The mean survival of the vaccine+chemotherapy group was significantly longer (26 ± 3.7 months) as compared to the mean survival of either the vaccine only or chemotherapy only group (17.9 ± 1.7 and 15.9 ± 2.1 months, respectively) (Fig. 5). Some patients administered the sequential therapy survived for three or four years, whereas there were no three-year survivors in the vaccine or chemotherapy group ([0048]). In addition, tumor regression was observed in three of the thirteen patients receiving the vaccine and chemotherapy treatment, apparently one of the first reproducible demonstrations of objective regression in an adoptive immunotherapy setting ([0047]). In view of the teaching of the

[1] Paragraph numbers refer to the published version of the present application, US 2007/0020297.

specification that "GBM diagnosis carries with it an average survival between twelve and eighteen months (with 90-95% [of] patients surviving less than two years), without the possibility of spontaneous remission or effective treatment," these findings of increased survivorship and tumor regression are truly remarkable. Again, this result is unexpected even in view of the combined disclosures of Vitiello, Knutson, and Friedman.

The Office action points out in several places (including at page 10) that "the instant specification discloses that there was NO significant difference in survival between the vaccine + chemotherapy group and vaccine group (Fig. 2; [00010], last sentence)." Applicants submit that this statement is an obvious error, and the specification has been amended to correct this error. As indicated in the Declaration of Dr. John S. Yu Under 37 CFR § 1.132, the same data was presented in the publication Wheeler et al., 2004, Clin. Cancer Res., 10:5316-26 (already of record) as demonstrating a statistically significant difference between the vaccine + chemotherapy group and the vaccine group ($P = 0.048$). Applicants submit that the results disclosed in Fig. 2 do show unexpected beneficial results of the claimed methods.

The currently pending claims are commensurate with the scope of the unexpected results disclosed in the specification. Claim 1 recites that the regimen of chemotherapy is administered to a mammal after glioma recurrence following administration of at least one vaccination of dendritic cells. Further, the chemotherapeutic agents recited in claim 1 were all used in the experiments described in the specification. See Fig. 7. Gliadel® wafers are a time-released encapsulation of BCNU, and Accutane® and Gleevec® are trade names of isotretinoin and imatinib, respectively. See paragraphs [0017] and [0040]. Based on at least applicants' surprising results, which are commensurate with the scope of the claims, applicants submit that the claims are patentable over Vitiello, Knutson, and Friedman. Applicants respectfully request reconsideration and withdrawal of the rejection for alleged obviousness.

Claims 6 and 7 were rejected as allegedly being unpatentable over Vitiello, Knutson, and Friedman, as applied to claims 1-3, 10, 11, 25, and 26 above, and further in view of Liu et al., 2003, J. Immunother., 26:301-312 ("Liu"). The Office action (at pages 16-17) presents Liu as

disclosing "a method of treating glioblastoma multiforme in a patient comprising administering autologous DC primed ex vivo with tumor antigen at a dose of $10X10^6$ to $40X10^6$ three times (p. 308, col. 2)." However, as discussed above, claim 1 (from which claims 6 and 7 depend) is patentable over the combination of Vitiello and Friedman based on at least the inventors' surprising results. Liu provides no teaching or suggestion to contradict this finding, at least because Liu does not teach or suggest the administration of chemotherapy following dendritic cell vaccination. Therefore, claims 6 and 7 are patentable over the combination of Vitiello, Knutson, Friedman, and Liu.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. This reply is being submitted with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 22862-0004US1.

Respectfully submitted,

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